NETWORK OVERVIEW

I. HVTN MISSION AND KEY CONCEPTS

In response to RFA-AI-05-001, this proposal is for the competing renewal of the HIV Vaccine Trials Network (HVTN), a comprehensive, multidisciplinary, global clinical trials platform spanning 4 continents. The proposal describes the HVTN's Leadership Coordinating and Operations Center (Leadership CORE); the HVTN Statistical and Data Management Center (SDMC), and the HVTN Network Laboratory Program. All 3 units of the HVTN are centered in Seattle, Washington, and are now co-located in a 100,000 square foot combined laboratory and office building within 2 blocks of the main Fred Hutchinson Cancer Research Center (FHCRC) campus. The HVTN Leadership CORE PI is Dr. Lawrence Corey; Dr. Judith Wasserheit is the HVTN Leadership CORE Director; the SDMC PI is Dr. Steven Self; and the Network Laboratory Program PI is Dr. Juliana McElrath.

The HVTN, established in 1999, has as its mission to fully characterize the safety, immunogenicity and efficacy of HIV vaccine candidates with the goal of making available, as rapidly as possible, a safe, effective vaccine for prevention of HIV infection globally. To date, the Network has conducted the majority of the published, presented or ongoing clinical trials of preventive HIV vaccines worldwide. In the process, it has gained tremendous experience with the challenges of running an innovative scientific organization that is global in reach, and which must combine the intellectual robustness and creativity of academia with the focus and infrastructure of industry. This proposal builds on the many scientific and operational lessons learned during the last 5 years and outlines some of the features that make the HVTN ideally suited to continue to spearhead the clinical evaluation of HIV vaccines.

The initial NIAID-supported HIV vaccine program, which started in 1986, existed as 2 separate clinical trials networks: the AIDS Vaccine Evaluation Group (AVEG), a contract organization that consisted of 6 US sites that were devoted solely to Phase I/II studies and the HIVNET Clinical Trials Group, a contract group that consisted of US and International clinical trial sites and investigators for Phase III clinical trials. The concept of the 2-network system was that after the initial Phase I/II evaluations were performed, one could utilize ongoing cohorts of subjects and "drop in" an HIV vaccine trial when a larger cohort was needed to evaluate vaccine efficacy. This was not a successful concept as only 2 international vaccine trials were performed in the decade of the HIVNET program. While the HIVNET program performed many significant trials in HIV prevention, this experiment illustrated that one could not just "drop" an HIV-1 vaccine trial into a non-US trial site without the infrastructure and understanding of the issues associated with such trials. HIV-1 vaccine trials were a "flash point" issue in communities in which HIV was a highly stigmatizing disease. Widespread concern about acquiring HIV-1 from the vaccine itself, the lack of discussion about the scientific safeguards on how such vaccines were constructed, and the issues of how diagnostic tests could or would differentiate responses to the vaccine from true HIV infection itself were of major concern within communities, health ministries, the popular press, and national assemblies. The lack of a cadre of respected scientists and regulatory persons involved in HIV-1 vaccine science resulted in the inability to initiate vaccine trials internationally.

The Division of AIDS recognized that if the field was to change, the dichotomization between early and advanced clinical development needed to be altered and a more integrated program initiated. Bearing this in mind, NIAID leadership approached Dr. Corey to reorganize the HIV vaccine clinical trials program and establish a new network called the HVTN. Several discussions and meetings were held about how a new network could overcome the deficiencies in HIV vaccine development. While the AVEG units themselves functioned smoothly once trials were initiated, novel vaccine products such as DNA vaccines or pox vectors were often plagued with prolonged delays in trial initiation because of lack of communication among developers, DAIDS, and the clinical investigators on what was needed to support Phase I trials. This often resulted in preclinical toxicity studies that did not support clinical trial designs, and subsequently required additional money and time to repeat such tests. It was also recognized that the clinical trials effort needed a stronger laboratory program. Animal models did not predict immune responses in humans, especially for assays of T cell responses. A contract laboratory program led by DAIDS was not effective in developing new assays or integrating itself into the AVEG clinical trials program; nor did a contract data management group provide the biometric support required to creatively develop vaccine trials or, more importantly, help in assay development. The new organization needed to develop a structure that allowed greater scientific exploration of novel assays as novel immunogens were developed. This was best achieved by integrating

more laboratory scientists into the clinical trials network and markedly enhancing the laboratory resources devoted to the vaccine program.

These discussions led to several concepts:

1. While the HVTN needed a centralized “corporate” administrative structure to provide the focal point for driving timely protocol development and implementation, it would continue to seek intellectual input from academic site PIs who directed the clinical trials units, and provided the scientific underpinnings of the Network. The clinical trial site PIs needed to be intellectually devoted to the field of HIV vaccines. They needed to know the biology of vaccine constructs in testing, follow the preclinical literature in vaccine development, and spend the major portion of their lives in HIV vaccine development. While such persons were already identified in the US, they required cultivation in international settings. Outside the US, such persons needed to be “discovered”, and clinical trials units built around them and sustained over time. Besides identifying a first generation group of investigators, programs needed to be identified to cultivate a “next generation” of international and US investigators interested and involved in the field. HIV vaccine development was going to be an extended march, not a sprint.
2. The laboratory program of the Network needed to be integrated into the Network’s clinical trials program. The shifting of the field from antibody to T cell–based vaccines required the development of new assays and technologies for measuring immune responses. The specimens from the Network trials were critical for developing and standardizing such assays, and the laboratories needed to innovate, as well as serve, the program. Placing the laboratories within the program under the Executive Committee would ensure this linkage and support, and marked increases in resources to the laboratory were needed to allow the development of new assays. This required the input and direct involvement of leading laboratory-based investigators in the Network.
3. The Network would establish a new biostatistical unit that would be integrated into the Network’s functions. This unit would provide expertise in both trial design and data management, as well as add a biometric unit to assist in analyzing newly developed laboratory assays.
4. The Network should develop a clinical trials protocol development process similar to that seen in industry. It needed to provide input on trial design during preclinical development to make sure toxicity testing matched the early clinical trial designs. These suggestions resulted in the development of the HVTN’s in-house scientific support, regulatory, community preparedness, and network evaluation programs, and the initiation of HVTN Development teams which would establish long term relationships with vaccine developers.
5. It was assumed that the vaccine field was going to expand greatly over the 5 years of the initial funding period. Rather than providing a fixed number of sites, it was felt best for the Network to expand when scientific opportunity required it to do so, and that much of this expansion needed to occur outside the US. Thus the Network built a fiscal and administrative infrastructure to initiate the process. Central to this was a defined process for reviewing future site expansion. The process for site expansion was peer reviewed. Its implementation would be left to the Network. To make it less insular, 2 outside experts would sit on the HVTN Executive Committee (EC), which oversaw the programmatic and fiscal aspects of the site expansion process.
6. The Network should have discretionary funds to facilitate vaccine testing. Funds for site expansion and discovery could and would be managed with the assent of DAIDS through the cooperative agreement mechanism. The HVTN should provide the fiscal oversight to new sites and hence develop financial systems that would allow similar core budgets to be established and then expand yearly as the scientific base for the site grew and the Network needs for utilizing the site in trials also grew. Other discretionary funds should be utilized to increase laboratory support through collaborations with investigators outside the HVTN and for other programs that the EC felt were critical to vaccine development. Expenditures in these categories over $250,000 should be vetted through an External Advisory Committee.

These concepts were all incorporated into the original network application, which was submitted and approved by the review panel in 1998. Most of the above concepts were prescient. Fortunately, most of the proposed solutions have fallen into the same category. The HVTN, which began as a network with 9 US sites, 1 international site in South Africa, and 2 subsites in the Caribbean, now comprises 12 independent US and 15 independent interna-

tional sites (Table 1). The site expansion process from 1999 to 2004 was all in non-US sites; HIV vaccine trials have been conducted at all of the international expansion sites. In 2005, 2 US sites were added to the HVTN for their ability to recruit and retain high-risk African American or Hispanic/Latino women into HVTN 502, an efficacy trial of the Merck replication-incompetent adenovirus type 5 gag/pol/nef vaccine. This trial started enrollment in February 2005 at HVTN sites, and is the first US-based NIH-supported efficacy trial of an HIV vaccine.

Table 1. HIV Vaccine Trials Units Supported by NIH 1998-2005

	AVEG	HVTN	
Site	PI (1998)	PI (2000)	PI (2005)
University of Alabama at Birmingham	M.Mulligan	M.Mulligan	**P.Goepfert**
Johns Hopkins University	D.Burke	D.Burke	**D.Burke**
Rochester	M.Keefer	M.Keefer	**M.Keefer**
University of Washington	L.Corey	J.McElrath	**J.McElrath**
Vanderbilt University	B.Graham	B.Graham	**P.Wright**
Saint Louis University	R.Belshe	R.Belshe	**R.Belshe**
Harvard University	—	R.Dolin	**R.Dolin/K.Mayer/M.Lally**
San Francisco Department of Health	—	S.Buchbinder	**S.Buchbinder**
University of Maryland/IHV	—	W.Blattner	**W.Blattner**
South Africa: Soweto	—	S.Karim	**G.Gray**
Columbia University/New York Blood Center	—	S.Hammer	**S.Hammer/B.Koblin**
Brazil: Rio de Janeiro, HESFA	—	M.Schechter	**M.Schechter**
Haiti: Port-au-Prince, GHESKIO	—	J.W. Pape	**J.W.Pape**
Trinidad and Tobago: Port of Spain, CCPRI	—	C. Bartholomew	**N.Jack**
Peru: Lima, Impacta	—	—	**J.Sanchez**
Peru: Iquitos	—	—	**J.Lama**
Thailand: Chiang Mai, RIHES	—	—	**T.Sirisanthana**
Botswana: Gaborone	—	—	**M.Essex**
South Africa: Cape Town	—	—	**L.-G.Bekker**
South Africa: Orkney	—	—	**G.Churchyard**
Brazil: Sao Paulo, Department of Health	—	—	**A.Kalichman**
Dominican Republic: Santo Domingo	—	—	**Y. Donastorg**
Jamaica: Ministry of Health	—	—	**P.Figueroa**
Puerto Rico: San Juan	—	—	**C.Zorilla**
Malawi: Blantyre, Q. Elizabeth Hospital	—	—	**T.E.Taha**
University of Illinois at Chicago	—	—	**R.Novak**
University of Pennsylvania	—	—	**D.Metzger**

Table 2 shows the pace of the addition of sites and the expansion of the Network's clinical trials activity over time and illustrates how the Network has melded site expansion with its scientific workload.

Much of the success of the HVTN in initiating Phase I trials at international sites under this grant period lies with its site PIs and the role these investigators play in the HVTN. The HVTN has had luminary in-country investigators who have learned the science of HIV vaccine development and have been committed to the clinical trials effort required to test a vaccine candidate. The time required from an international PI is enormous. They must be accomplished managers of their HVTU staff and advocate at their institutions for space for the vaccine unit. They also must educate their peers and communities about HIV vaccines and the investigative process required to develop an HIV vaccine and also explain both the science and policy issues to their national AIDS committees, Ministries of Health, and National Assemblies. Bringing US-made and US-funded products into international settings has become more complicated geopolitically as well as scientifically. The strength of the HVTN is that its face in international centers is its site investigators. Much of the HVTN's success in getting early phase HIV vaccine trials successfully into countries is because of the scientific stature and credibility of its site PIs.

Since its inception in 1999, the HVTN has initiated 20 trials, involving more than 2,200 subjects, performed in 17 clinical trial sites, in 10 countries. Thus, the HVTN has accomplished its primary mission of developing a functioning and effective global clinical trials network. It has continued the original success of the AVEG of performing quality Phase I/II trials of vaccines in the US while at the same time implementing a global vaccine clinical trials program that is currently conducting vaccine trials from first-in-human to true efficacy trials. It has established novel fiscal, administrative, and scientific leadership structures and programs that have provided the mechanism to undergo this transformation in an unprecedented time frame, and with stringent fiscal and regulatory procedures. It has done this as a team, requiring the input from all its members and its entire administrative staff and in strong partnership with DAIDS. Vaccine trials are designed and implemented at a record pace. The number and quality of the clinical and laboratory assessments are

Table 2. No. of HVTN protocols, participants, and sites, 1999-2005.

	Year						
	1999	2000	2001	2002	2003	2004	2005 (est.)
Protocols opened	na	1	2	2	6	7	9
Protocols enrolling	na	1	3	4	7	12	14
Protocols in follow-up	na	1	3	5	11	14	12
Participants	177	69*	389	282	364	1309	2420
US sites	6	6	10	10	9	10	12
non-US sites	0	0	3	4	5	7	13

na: data not available.
*55 enrolled in HIVNET, 14 in HVTN.

higher now than at any prior time in the program's history.

While the accomplishments are many, a plethora of challenges remain in HIV vaccine development. There are many areas of structure, organization, and scientific focus that must, and will, improve. This application reflects an intense series of discussions that went into both the scientific and organizational development of the proposal. As discussed below, the Network has many fora in which its scientific agenda and focus are reviewed. It also has 2 scientific external advisory boards: one called the External Advisory Committee, which evaluates the program yearly; and a Laboratory Sciences Advisory Committee, which reviews the laboratory aspects of the studies, including the results from trials, initially quarterly and now semiannually. It also has a Global Community Advisory Board; selected members sit on each of these HVTN bodies.

In preparation for this reapplication, the HVTN conducted 2 separate 2-day meetings with its advisory panels, which were expanded to include other outside experts, to redefine the mission and processes of the HVTN. The scientific agenda and programmatic areas of past and future activities were outlined and debated. From these discussions emanated several important concepts central to the Network application.

- The HVTN has been, and will remain, focused on and dedicated to testing vaccines for prevention of HIV globally. Thus, while the Network will collaborate, often extensively, with groups involved in the development of vaccines for use in HIV-infected persons (commonly called "therapeutic vaccines"), interruption of maternal-fetal transmission, and decreasing the acquisition of HIV-1 in neonates or children via breast milk, the HVTN's priority will be to define the safety, immunogenicity and efficacy of candidate HIV vaccines in HIV-negative adult and adolescent populations.
- The Network laboratory has played a pivotal role in the global HIV vaccine field. It is the first, and at the moment only, NIH-supported laboratory that has developed validated assays for use in qualifying potential HIV vaccines for efficacy studies (both for T cell and neutralizing antibodies). In parallel, the SDMC has played a central role in advancing study design and statistical analysis methods for HIV vaccine trials and, in the past funding cycle, has made major contributions to methodologies for the evaluation of CTL-based vaccine candidates. This scientific synergy among the clinical trialists, laboratory and statistical faculty of the HVTN is especially important as the quest to define correlates of protection for T cell–based vaccines is now upon us. Novel assays and reagents, statistical designs, and collaborations will be required to maximize the information from the HVTN Merck and planned VRC efficacy trials. These issues are discussed extensively in the Leadership Research Plan.
- The Network has developed a standardized Phase I program defining the initial safety and immunogenicity of a candidate vaccine. This is an important programmatic feature for vaccine development, as to date all vaccine candidates that have gone to advanced clinical development have been reformulated after the initial Phase I trial. As the field develops more immunogenic vaccines it is now crucial to rapidly implement phase II trials, especially combination vaccine trials or head-to-head comparative trials, to "qualify vaccines" for further testing.
- The HVTN is an experienced collaborator. The Network has established private-public partnerships with numerous industry collaborators. The progression from the initial joint trial (HVTN 050/ Merck 018) to a proof-of-concept efficacy trial (HVTN 502/ Merck 023) speak to the success of this partnership. The extensive collaboration between the HVTN and the NIAID Vaccine Research Center (VRC) has been a model for integrating a clinical trials network with a publicly funded vaccine developer. This collaboration will be solidified and augmented with the impending launch of the first VRC efficacy trial, which will involve the HVTN, International AIDS Vaccine Initiative (IAVI) and the US Military HIV Research Program (USMHRP).
- The HVTN has extensive experience collaborating with DAIDS and DAIDS-supported research networks. During the last funding cycle, the HVTN joined the HPTN, the ACTG, and the PACTG to support a new position, the HIV Clinical Trials Networks Leadership Coordinator, charged with facilitating internetwork collaboration, and standardizing processes across networks. The HVTN staff also participates actively in the Partnership for HIV Vaccine Evaluation (PAVE). The HVTN Network principals have been instrumental in preparation for joint PAVE trials by setting uniform standards for site development, specimen processing and shipment as well as assay validation.

- The HVTN is dedicated to conducting trials of HIV vaccines among both men and women in a broad range of racial and ethnic populations and geographic regions. The HVTN will also conduct trials among both injection drug users (IDU), adolescents, and volunteers at risk for heterosexual and homosexual transmission of HIV infection.
- The HVTN's program of site expansion has proven very successful in connecting the science of vaccine development with the sites both by involving site PIs in state-of-the-art HIV vaccine research and by investigating vaccine safety and efficacy in populations most in need of a preventive vaccine. Two critical factors drive the need for continued HVTN leadership in the expansion and management of its clinical trial sites and laboratory capacity. First, the global HIV pandemic will continue to evolve and change, putting new populations at risk. Second, with increased efforts in pre-clinical vaccine development, the pipeline for novel vaccines and the number of vaccine trials that will be conducted will increase markedly over the next 5 to 7 years. It is critical that the Network include a mixture of sites capable of accomplishing the full range of scientific goals, from sites capable of doing first in human clinical trials of novel vectors, to sites that can efficiently conduct HIV vaccine licensure studies. Thus, the site development process is a critical component of this Leadership CORE application.
- The Network has achieved a data management system and organization that is of the highest quality. Data quality begins at the study sites and the HVTN has developed training and review processes which meet all regulatory standards and ensure quality data from a variety of technologically diverse international settings.
- The Network is committed to development of sustainable scientific and clinical trial site capacity in a way that is supported both by the scientific community and by the greater community of potential trial participants and individuals at risk. This concept is fundamental both to our ability to conduct ethically sound, scientifically rigorous trials in the near term, and to our broader ability to advance HIV vaccine research efficiently and cost effectively in the medium and long term. The HVTN has created a laboratory of immunological excellence at the National Institute for Communicable Diseases in Johannesburg under the direction of Clive Gray and Lynn Morris. This collaboration will continue and be strengthened during this grant period.
- Much of the success of the HVTN lies with its site PIs and the role they play in Network operations. Our broad commitment to them will continue to be reflected by inclusion of non-US investigators in HVTN scientific leadership roles, and proactive strategies to attract new, talented investigators from around the world to work in HIV vaccine clinical trials. In parallel the Network will launch a range of activities geared towards trial participants and the larger community. These will include the following: extensive community education efforts at each site; the continued support of Community Advisory Boards (CABs); and establishment of a program to ensure access to antiretroviral therapy (ART) for volunteers who become HIV infected during HVTN vaccine trials.
- The HVTN derives its scientific and organizational strength from the scientific input of its members, with its current composition of 27 clinical trial sites in 15 countries.

The review panels helped define the scientific agenda of the Network. The Specific Aims of the HVTN application are the following:

Specific Aim 1: To develop and maintain a Clinical Trials Network that will provide an objective and transparent platform to evaluate the safety, immunogenicity and efficacy of candidate HIV vaccines for the prevention of HIV infection in adult and adolescent populations globally.

- To perform first-in-human clinical trials of novel candidate HIV vaccines to evaluate their safety and immunogenicity, and define the optimal regimen characteristics (including dose, route, and schedule) of the individual vaccine candidate(s).
- To develop and maintain a state-of-the-art laboratory program to execute protocol-related endpoint laboratory studies in a GLP setting that will provide objective measurements of vaccine immunogenicity. This includes:
  a) providing the administrative structure to carry out an integrated laboratory program of PBMC collection, processing, storage, and analyses;
  b) conducting validated endpoint immunologic assays in HVTN Phase I-III clinical trials;

c) identifying HIV efficacy and the immune responses that correlate with vaccine-induced protection in Phase IIB-III clinical trials;

d) developing new assays to evaluate innate and mucosal immunity as well as antivector responses that may augment or dampen vaccine efficacy; and

e) implementing a rigorous QA/QC and operations program for the HVTN laboratory.

- To evaluate vaccine approaches designed to produce mucosal immune responses. Develop vaccine regimens that will optimize immune responses at mucosal surfaces. This may include the definition and quantitation of T cells that home to mucosal surfaces, cellular, antibody and innate responses that may inhibit the spread of HIV across genital mucosal surfaces or contain HIV replication within gut lymphoid tissues. (This section of the grant may also apply to NICDR funding)
- To perform clinical trials of novel adjuvants, assess the unique innate or adaptive immune response elicited by such adjuvants and utilize these adjuvants with HIV-1 immunogens to improve the breadth, quality, and magnitude of the immunological responses to HIV-1 vaccines and to assess if such responses improve vaccine efficacy, acceptability, and cost.
- To develop an effective community education program that will enhance the enrollment and retention of populations at high risk for acquisition of HIV in the US and internationally. Education of communities at risk about HIV-1 vaccines, the process of clinical trials and the role that communities play in design, implementation, conduct and review of clinical trials is essential to fulfill the mission of the HVTN.

Specific Aim 2: To conduct head-to-head comparisons of candidate vaccines to determine whether there are competitive advantages in safety and/or immunogenicity between the candidates, especially products that fall into a class of agents such as pox virus vectors, replication defective adenovirus vectors or DNA plasmids.

- To design and conduct clinical trials of rational combinations of vaccines in order to develop maximally safe and immunogenic vaccine regimens.

Specific Aim 3: To perform a series of Phase II trials in populations throughout the world to determine if a vaccine candidate or vaccine regimen “qualifies” for further efficacy evaluation. This evaluation should utilize predetermined criteria for advancement of the vaccine into a defined population that may differ in geographical location, age, social characteristics, or definable genetic characteristics; and assess the role of prior vector immunity in the immune response.

Specific Aim 4: To develop standardized risk reduction counseling methods that are applicable across HVTN sites and standardized approaches to measurement and monitoring of HIV risk behaviors during vaccine trials.

Specific Aim 5: To design and conduct a program of HIV vaccine efficacy trials in men and women at risk of sexual and/or parenteral acquisition of HIV throughout the world that provides rigorous tests of critical scientific concepts for the development of HIV vaccines, and ultimately delivers sufficient characterization of the safety and efficacy of a candidate vaccine to enable its licensure.

- To define endpoints for use in HVTN efficacy trials that provide a sensitive and reliable indication of vaccine effects on the clinical course of HIV infection.
- To develop standardized guidelines to initiate antiretroviral therapy (ART) in the context of HVTN trials and to develop a standardized protocol to evaluate ART regimens among persons in HVTN trials who acquire HIV infection in order to develop information on whether vaccination improves the virological and immunological response to ART.

Specific Aim 6: To develop the laboratory and statistical approaches to optimize the design of clinical trials that will define potential correlates of protection within HIV vaccine efficacy trials. This includes assessments of the immune responses to vaccines prior to and after acquisition of HIV-1; the effects of the vaccine on influencing the phenotypic or genetic characteristics of the infecting viral strain; and the potential role host genetics play in reducing acquisition or set point viremia.

Specific Aim 7: To develop a clinical trials program that will evaluate the safety and effectiveness of vaccines in advanced clinical development in IDU populations.

Specific Aim 8: To develop a clinical trials program that will evaluate the safety, immunogenicity and effectiveness of HIV preventive vaccines in adolescents.

Specific Aim 9: To develop and implement an integrated strategy within the HVTN efficacy trials program for the assessment of indirect and overall effects of CTL-mediated HIV vaccine candidates on HIV transmission at individual and population levels.

Specific Aim 10: To continue to develop and support mutually beneficial coordination and collaboration between the HVTN and relevant NIH networks, federal agencies and non-governmental research organizations to advance the highest quality HIV vaccine research, with optimal efficiency and cost effectiveness.

II. HVTN ORGANIZATIONAL STRUCTURE

The HVTN has evolved considerably in its structures and policies since its inception in 1999. The proposed organizational structure of the HVTN in this grant period builds on the strengths of and lessons learned from the existing structure and is the result of detailed assessments and discussions conducted this past year by the Leadership Group and external consultants. These discussions, involving US and international investigators, Seattle-based HVTN and Bethesda-based DAIDS staff, sought to optimize the structure of the Network to support the expanded number and complexity of vaccine trials anticipated during the upcoming 7-year grant period. This section summarizes the role, composition and functional relationships of the HVTN's committees, working groups and Leadership components.

The functional centerpiece of the organization continues to be the US and international HIV Vaccine Trial Units (HVTUs). To accomplish the scientific agenda discussed in the Research Plan, HVTUs both in the US, and internationally must meet at least 1 of the following 3 criteria: 1) provision of scientific leadership, 2) capacity to enroll large numbers of participants in trials, and 3) access to populations that are particularly high priority for inclusion in HIV vaccine trials, ie, people of color (especially women of color) in the US, and adolescents and IDU at international sites. Although some sites may meet all 3 criteria, we anticipate that, in some cases, some sites with more limited expertise will be needed to achieve the appropriate balance of site capacity. An organizational chart of the proposed structure of the Network is presented in Figure 1.

The Network will be led by a Scientific Steering Committee (SSC), the HVTN counterpart to the Executive Committee called for in the RFA, that works through and is supported by 9 scientific and resource committees, and 6 working groups. The HVTUs, SSC, and the HVTN committees and working groups are supported by the three tightly linked components of the HVTN's Leadership Group, the SDMC, the Laboratory Program and the Leadership CORE. The HVTN also has 4 very active advisory committees or boards (the External Advisory Committee, the Safety Monitoring Board, the Global Community Advisory Board, and the Laboratory Sciences Advisory Committee) that assist the SSC by providing recommendations on critical scientific, operational and community issues.

A. Scientific Steering Committee (SSC)

The governing body of the HVTN is the Scientific Steering Committee (SSC), which serves as the Executive Committee of the HVTN. Its members, which include the senior HVTN leadership plus 2 representatives from DAIDS and 2 external advisors, provide scientific, administrative, fiscal and programmatic leadership and governance, including the following activities:

a. establish and approve overall policies and procedures;

b. approve a scientific agenda, prioritize the research questions, and oversee the research activities of Network committees;

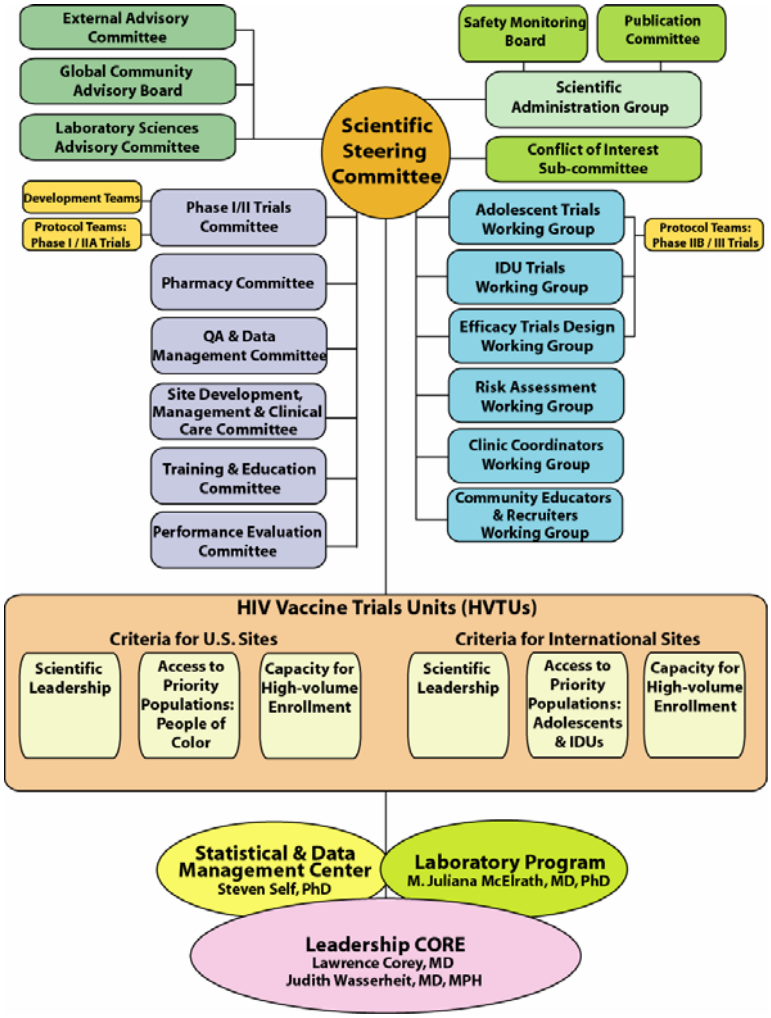
c. approve expenditures, including funds for the Leadership CORE, SDMC, the Laboratory Program, and discretionary funds, and provide recommendations to DAIDS regarding appropriate funding of clinical trial units;

d. oversee the site expansion and development process;

e. approve standards for the clinical care provided to trial participants who become HIV infected;

f. establish performance and quality standards for all sites and members, including the SDMC and CORE; review Performance Evaluation Committee (PEC) reports; and recommend resource reallocations;

Figure 1. Organizational structure of the HIV Vaccine Trials Network.



g. provide an annual report to DAIDS that outlines HVTN programmatic initiatives and accomplishments;

h. oversee conflict of interest issues;

i. determine disciplinary action for sites and members, including recommendations to the NIAID regarding site funding; and

j. approve the Governance Principles (bylaws) of the HVTN.

The membership of the SSC includes the leaders of each of the components of the Leadership Group, the Phase I/II Committee Chair and elected representatives of the Global Community Advisory Board and the Clinic Coordinators Working Group. Two US PIs and 2 international PIs will serve as elected representatives of the HVTU investigators. Dr. Corey, the HVTN Principal Investigator and Dr. Wasserheit, the HVTN Director, will serve *ex officio* as SSC Chair and co-Chair, respectively, for the duration of their appointments under the grant period (7 years). Similarly. Dr. Self, the Head of the SDMC, Dr. McElrath, the Head of the Laboratory Program, and Dr. Michael Keefer, the Associate Director for Scientific Administration, will be voting members of the SSC for the full term of their HVTN Leadership Group participation. SSC membership will be augmented by 2 DAIDS representatives and two external advisors to ensure strong, complementary expertise and perspective. External Advisor members, working group representatives, and US and international at-large PI members will serve 2-year terms with the option for reappointment. The proposed structure is similar to that of the current, successfully functioning SSC.

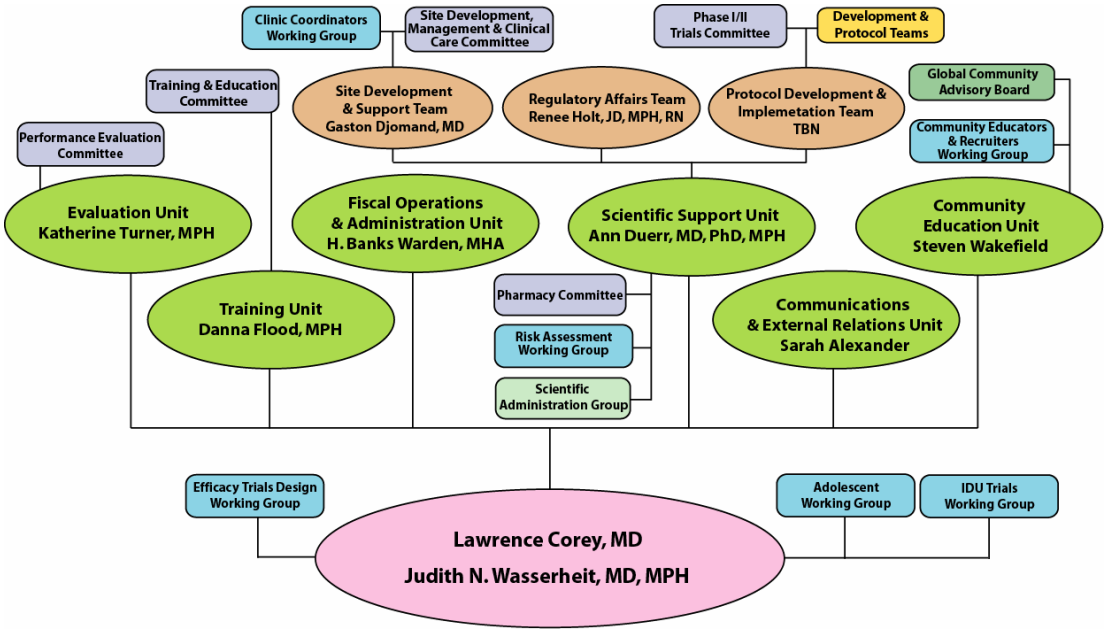
The SSC meets by conference call on the first Monday of each month with ad hoc calls as needed. The Committee convenes 1 conference each year of the entire HVTN membership, HIV vaccine developers, HIV vaccine research partners, and the larger scientific community in the Washington DC metropolitan area. The HVTN will work closely with DAIDS and OAR in the development of these conferences. Face-to-face meetings of the SSC are held at the HVTN conference and at least 1 other time a year as a forum for discussion of trial data or emerging scientific, operational, or policy issues. The current HVTN Full Group Meeting is attended by over 500 persons yearly. It has been a focal point for defining the key issues in HIV vaccine development. Its plenary sessions are translated into Spanish, French and Portuguese.

1. Scientific Administration Group (SAG)

While fiscal decisions relating to the Network are discussed in full committee, scientific discussions including prioritization of protocols and resources require more than monthly meetings, and as such the SSC has established a working subcommittee to provide day-to-day scientific oversight to the HVTN. This group is called the Scientific Administration Group (SAG). The SAG serves as the managerial arm of the SSC and provides guidance regarding the appropriate allocation of Network resources, including suggestions for modifications of protocols and projects to increase cost efficiency. The SAG is chaired by the Associate Director for Scientific Administration, Dr. Keefer, and co-chaired by the Associate Director for Scientific Support, Dr. Ann Duerr. Membership includes the SSC Chair and Co-chair, Drs. Corey, and Wasserheit; the SDMC Principal Investigator, Dr. Self; the Laboratory Pro-

gram Principal Investigators, Drs. McElrath, and Kent Weinhold, the HVTN COO, Mr. Banks Warden; the Phase I/II Chair, Dr. Scott Hammer; the Chair of the Efficacy Trials Design Working Group, Dr. Susan Buchbinder; a site PI, currently Dr. Raphael Dolin; and a representative from DAIDS. The SAG is convened every other week by conference call and reports to the SSC each month during the SSC conference call. The frequent meetings of the SAG means that senior leadership is constantly managing the HVTN and providing input proactively into its scientific and fiscal agenda.

Figure 2. Organizational structure of the HVTN Leadership Coordinating and Operations Center.



B. The Leadership Coordinating and Operations Center

The Leadership CORE provides overall direction and coordination for the HVTN. It assumes primary responsibility for protocol development and implementation, site development and support, regulatory compliance, community preparedness, communication and external relations, training, administrative and fiscal management, and monitoring performance of all Network components. The organizational structure of the Leadership CORE (Figure 2) reflects these 8 functions, and supports the committees and working groups described in detail below.

1. Scientific Support

The concept of full time professional staff devoted to protocol design, development and implementation has been extremely successful. The HVTN Scientific Support Unit (SSU) coordinates protocol development, provides assistance to new and mature vaccine trial sites, and supports the smooth implementation of protocols in HVTUs across the Network. All employees of the SSU devote full time to the HVTN effort and hence provide a focused, dedicated staff with defined responsibilities and functions. The SSU consists of 3 teams—the Protocol Development and Implementation Team (PDIT), which includes Protocol Team Leaders (physicians or PhDs with clinical trials experience) and Protocol Development and Operations Coordinators; the Site Development and Support Team (SDST), which includes Site Coordinators; and the Regulatory Affairs Team, which includes the Regulatory Affairs Monitor and 2 Regulatory Associates—as well as a nurse with extensive experience in HIV care and safety monitoring.

The HVTN has been able to complete protocols for review by DAIDS and then submission to the FDA within 40 days of formation of the full protocol team, considerably faster than most pharmaceutical companies. The “glue” for this process is the professional staff of the SSU. The HVTN Leadership CORE, SDMC and Laboratory Operations Group work closely to initiate trial implementation. Preparation includes assignment of trial sites and allocation of participant slots, a procedure coordinated by Dr. Keefer and by Dr. Margaret Wecker of the Protocol Development and Implementation Team, in collaboration with representatives from the SDMC and Laboratory Program. These allocations are based on the distribution of workload within the Network, as well as special considerations that may limit the location and number of participating HVTUs, such as HIV vaccine subtype, vaccine stability issues, need to recruit specific at-risk populations, specialized expertise of a PI or laboratory, and investigator participation on the Development or Protocol Team.

Trial sites receive the protocol at the time it is submitted to the FDA. Necessary translations into French, Creole, Spanish, or Portuguese are conducted centrally through an HVTN contractor. The site PI is responsible for obtaining local (institutional, regional, and/or national) IRB approval and local Institutional Biosafety Committee (IBC), with assistance from the SSU's Regulatory Affairs Team. This Team also assists sites in meeting other regulatory, Network, and DAIDS requirements for clinical trials, reviewing site consent forms for regulatory sufficiency and ensuring that sites have adequate regulatory and GCP elements in place before beginning an HVTN trial. During the course of trial conduct, the Unit, in conjunction with the SDMC protocol statisticians, provides the DAIDS regulatory contractor with materials sufficient for annual IND reports and for the biosafety reporting requirements of the NIH Office of Biotechnology Assessment (OBA), if required. A detailed review of HVTN protocols and operations is described in the application.

The HVTN SSU also directs a Site Development and Support Team (SDST) that has provided the staffing needed to bring new sites into the HVTN and to monitor participant accrual and retention rates at the HVTUs. The HVTN process for site development and support is discussed in the CORE Research Plan.

2. HVTN LEADERSHIP FISCAL OPERATIONS & ADMINISTRATIVE MANAGEMENT

The Fiscal Operations and Administration Unit (FOAU) provides fiscal and administrative management and support for all components of the HVTN. This group is led by Mr. Banks Warden, the HVTN COO. This unit has created specially designed systems for financial forecasting and reporting, cost accounting, contract negotiation and monitoring, conference call management, travel management, conflict of interest reporting, and regulatory compliance related to the implementation of HIV/AIDS applied research and vaccine testing. The FOAU utilizes the FHCRC's state-of-the-art financial management system to produce management reports employing historical trend analysis, budgets, and operating plans to produce financial forecasts for each annual grant renewal and beyond. This allows the HVTN PI and Director, the SSC and DAIDS to make timely decisions regarding efficient allocation of fiscal resources. The fiscal unit translates each protocol into a budget, which is based on a series of standardized metrics. These include standardized assessments of clinic visits and costs, such as staff hours, costs for each lab test, blood draw and procedure, physician and nurse hours per volunteer, and cost per volunteer, as well as screening-to-enrollment ratios. The protocol-specific budget is melded with the core budgets and assessments are made of capability and costs across trials within an HVTU and for each specific trial across HVTUs. Each of these budgets is then reviewed by senior members from the Leadership CORE, SDMC and Laboratory Program, to ensure that the fiscal plans are thoroughly coordinated, effectively designed and timed to contribute to the progress of the Network, before being submitted to the SSC for final review and approval. Formal contractual agreements are currently developed by the FOAU with all international sites, and the domestic sites funded by the Leadership CORE. These agreements include the milestones and budget parameters approved by the Director and the SSC.

The HVTN PI and Director routinely monitor the reports from each trial and site relative to cost, performance, schedule and scope. Significant findings are reported to the SSC and appropriate committees. Decisions to terminate or significantly modify a study or site are made by the SSC, in consultation with DAIDS.

3. COMMUNITY PREPAREDNESS AND EDUCATION

The HVTN has worked to build partnerships that result in a broad base of community support for vaccine clinical trials. Community members, particularly potential trial participants and individuals from the populations from which participants will be recruited, have played and will continue to play an integral role in the governance and conduct of HVTN trials. The Community Education Unit (CEU) of the HVTN Leadership CORE, led by Mr. Steven Wakefield, a nationally respected leader in community education and mobilization for HIV prevention and research, assists site PIs and staff in the development and implementation of community education plans. The CEU coordinates community education efforts across the global Network. CEU staff also support CAB members' participation in the development and implementation of the Network's scientific agenda and in facilitating communication from the HVTN to the community and vice versa. HVTN CABs comprise a broad cross-section of the community including people living with HIV/AIDS, non-government organizations, community activists, community-based HIV organizations, professionals involved in providing HIV services, religious groups, and trial participants. As all are volunteers, a central support unit for their needs and efforts is essential. A detailed discussion of the role community members play in the HVTN is reported in Specific Aim 1.5. of the CORE Research Plan.

4. COMMUNICATIONS AND MEDIA RELATIONS

With an expanding portfolio of vaccine trials and the initiation of efficacy trials, there is a need for professional expertise to assist HVTUs in development and implementation of locally appropriate messages about HIV vaccine trials. The HVTN was very lucky to attract as the leader of this effort Ms. Sarah Alexander, who completed her 15-year career in Microsoft's Corporate Communications by serving as the International Corporate Issues Manager for the Law & Corporate Affairs Group. She is a superb translator of science and policy for the HVTN and, as you might expect, is facile with electronic forms of communication such as web-based publications and communication.

One of the key functions of the HVTN Communications Unit is to liaise and coordinate with DAIDS' HIV Vaccine Communications Campaign. Ms. Alexander will continue to serve as a member of the Campaign Steering Group. The DAIDS-HVCC, plays a significant role in conditioning the environment in US communities where the HVTN conducts vaccine trials. Close message integration between the HVCC and the HVTN allows local efforts to leverage the work and placements of the national campaign. With the development of pluripotent sites, complementary messages will be critical. Therefore, the HVTN will share with other DAIDS-funded networks communications training modules on message development, materials development, media relations, and crisis planning and execution.

5. MANAGERIAL STRUCTURE

The HVTN has also developed many managerial mechanisms to coordinate the diverse collaborations and programs of the Network and ensure operational oversight and accountability (described in the CORE Research Plan). One of the principle fora is a twice-monthly 2-hour senior management team meeting that is attended by the PIs of the 3 Network Leadership components and key operations directors, committee chairs, and lab directors who join by phone. This meeting is led by Drs. Corey and Wasserheit and is a problem-solving forum to discuss and resolve any and all Network issues as they arise. Standing items include a brief review of each protocol and site to outline progress and problems. The meeting is just one example of the proactive stewardship and time commitment of each of the HVTN leaders toward making the HVTN an innovative and efficient network. During this grant period, a standing monthly meeting of Drs. Corey, Wasserheit, McElrath, and Self will also be initiated to ensure consensus and discussion of the HVTN's positions for the new Inter-Network Management Committee. The HVTN PI and Director have a regularly scheduled call with the DAIDS VPRP Leadership during this funding period; Drs. McElrath and Self will be added to this call.

C. The SDMC – Statistical Collaboration and Methodologic Research

The Statistical Center for HIV/AIDS Research & Prevention (SCHARP) of the FHCRC and affiliated faculty at the University of Washington provide statistical, operational and data management expertise for HIV vaccine and prevention trials.

An overarching goal of the HVTN SDMC is to provide statistical collaboration of the highest quality for all HVTN-related research endeavors. To ensure that statistical issues are identified and addressed throughout Network activities, faculty-level biostatisticians are integral members of all vaccine development teams, protocol teams, laboratory science research, network scientific reviews, and oversight committees. This comprehensive engagement in the Network research program provides HVTN statisticians with a broad perspective and allows identification of common statistical themes around which HVTN study designs and analytic methods can be standardized. Examples of this programmatic-level of statistical collaboration include standardized design schemas for HVTN Phase I/II trials, standardized methods for the analysis of immunogenicity endpoints in HVTN trials, and the statistical rationale for test-of-concept vaccine efficacy trial designs. These methodologies are operationalized in the form of SOPs and templates that prescribe statistical sections of trial protocols and statistical analysis plans; standardized and validated computer programs for study design calculations, data analyses and generation of routine study monitoring reports employed by the HVTN SDMC.

Broad engagement by SDMC statisticians in Network activities also provides the opportunity to identify and prioritize problems for which standard statistical solutions are not available or, if available, are not optimized to meet HVTN needs. SDMC statisticians engage in a robust program of biostatistical methodologic research driven by this stream of problems that have highest priority to and direct impact on HVTN research activities. A system of statistical working groups, communicating directly with HVTN clinical and laboratory researchers, are organized around

the more substantial of these methodology problems. These working groups provide an effective mechanism for efficiently developing, evaluating, implementing and publishing novel statistical methods for addressing these problems. Examples of this methodological research include methods for evaluating primary ELISPOT endpoints in Phase I vaccine trials, methods for evaluating HIV vaccine effects on disease progression in efficacy trials, and "sieve analysis" methods for evaluating if and how vaccine efficacy to prevent HIV infection depends on genotypic/phenotypic characteristics of HIV (references can be found in the CORE Research Plan).

Problems that are rich enough to form the focus of a larger methodology research program often lead to the development of applications for independent funding. This mechanism is ideal in that it effectively leverages Network-based funding.

1. SDMC Structural Organization

The SDMC organization is characterized by:

- SCHARP Study Teams led by project managers who manage SDMC aspects of the trial from implementation through final analysis. The project managers work directly with their counterparts in the Network CORE and Lab offices and a SDMC Senior Statistician assigned to each study;
- Study Teams are overseen by Network affiliated Senior Project Managers, very experienced clinical trialists who provide technical direction to the Study Teams, provide rapid problem solving and are a key liaison to their counterparts in the CORE. The Senior Project Managers have direct access to the Executive Leadership Group (ELG) of SDMC, to speed problem solving and enhance the responsiveness to the networks.

2. SDMC Functional Organization

SCHARP is the SDMC for the HVTN and the HIV Prevention Trials Network (HPTN), and is applying to be the SDMC for the Microbicide Trials Network (MTN). Functionally, the SDMC is divided into 4 Departments with 12 Sections (Figure 3). Staff from 6 groups outside the project management department comprise the Study Team: statistical sciences, statistical analysis and reporting, data operations, operations programming, clinical data reporting, and technical documents. The other Sections support non-study-specific aspects of SDMC activity, eg, IT support, fiscal oversight, and administration.

a. The SDMC Internal Study Team

The SDMC internal Study Team will serve as the key cross-function organizational unit working within the SDMC and be a sub-unit of the larger HVTN study team with includes members from CORE and Lab. The SDMC Study Team manages those aspects of the study that occur within the SDMC (CRF design, clinical database and clinical monitoring set up, randomization system development, standard report setup, etc.), and works with the HVTN team to assure that other aspects of the trial necessary for start up are accomplished in a timely fashion.

b. Studies Department

This small group consists of the Senior Project Managers, Project Managers and Project Assistants. Senior PMs are experienced clinical trial specialists who oversee a cluster of trials within the same Network. Project Managers are given the authority and responsibility to lead the team in aspects of trial design, operation and closeout that are the responsibility of the SDMC. Responsibilities include: (**1**) ensuring that SCHARP meets its obligations in accordance with Good Clinical Data Management Practices (GCDMP); (**2**) ensuring timely development of DataFax setup, randomization system, product labeling, study database, DataFax/SAS edit checks, CRF and study materials, study-specific training materials/plan, safety reporting system, statistical analysis/reporting plan, specimen collection and labeling, shipping and storage plans, laboratory results data receipt procedures and study closeout; and (**3**) serving as primary SDMC operational liaison with affiliated programs and institutions (eg, CORE, Network laboratories, DAIDS, protocol chair, and manufacturer).

c. Statistical Science Department

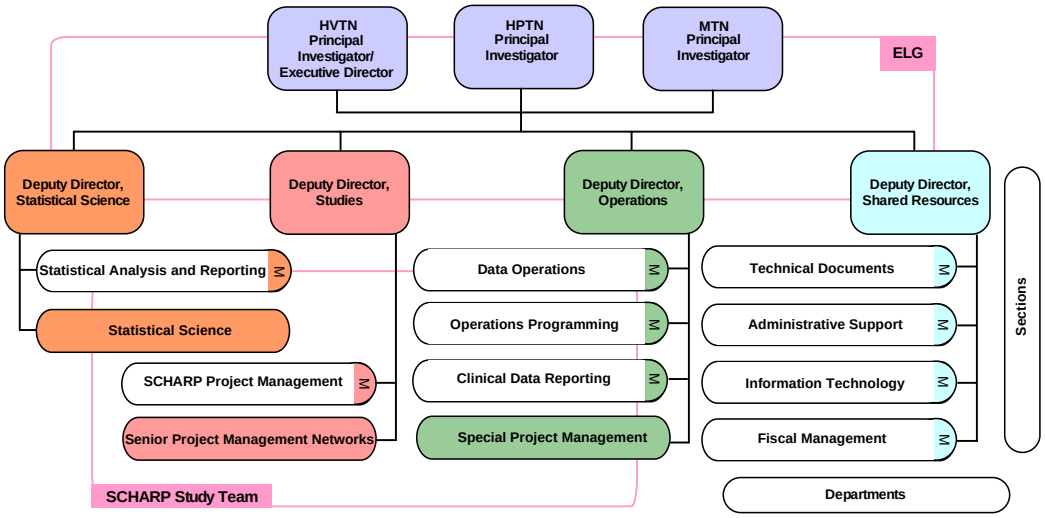
The Statistical Science Department is composed of 2 Sections. Faculty Statisticians hold either University of Washington or FHCRC faculty appointments. The Statistical Analysis and Reporting Section includes the Statistical Research Associates (SRAs), who are masters-level statisticians. This group **a**. provides biostatistical leadership on research directions and study design; **b**. develops innovative, effective, and efficient design and analytic methods for HIV prevention studies; **c**. performs analysis and interpretation of study data in collaboration with

Network investigators; and **d**. provides statistical input to the development, implementation and operation of data management and quality control procedures.

d. Operations Department

The Operations Department consists of 4 Sections. Members of these Sections include all the staff responsible for data entry and data quality control, the protocol programmers, the clinical data monitoring staff and the special projects section. Special project management is staffed by a small number of senior project managers responsible for the development of systems, tools, documents, etc. that are not study related. This Department: **a**. performs all aspects of data flow management—from the time data enters the SDMC as a DataFax image to the time data resides in the SAS database including performing all data entry, producing data QC reports to the sites and resolving errors; **b**. provides database management and production of routine study monitoring reports; **c**. develops and maintains clinical safety monitoring programs and safety reports; **d**. develops and supports the statistical database and the laboratory specimen tracking system, **e**. monitors clinical safety reports for Protocol Safety Teams and codes adverse experiences reported on CRFs using MedDRA; **f**. provides Special Project support.

Figure 3. SDMC organizational structure.



e. Shared Resources Department

The Shared Resources Department contains Sections that support departmental infrastructure. The responsibilities include **a**. providing administrative support including personnel, payroll and facilities management; as well as fiscal oversight; **b**. designing and producing all study materials, including CRFs in 17 different languages; **c**. designing and maintaining the internal Web site and support Network specific web servers; **d**. installing and maintaining all work stations and servers required to support the DataFax systems as well as the PC and UNIX Network within the SDMC; **e**. building and maintaining data security requirements, including systems responsible for daily data backups and firewall construction and maintenance; and **f**. deploying and maintaining DataFax and Internet fax-relay systems at all US and non-US sites.

D. The Laboratory Program

The HVTN Laboratory Program will provide the leadership, scientific expertise and operational capacity of the HVTN laboratories. The program provides oversight for the site-associated safety and specimen processing labs, specimen redistribution and repository labs, protocol immune and viral monitoring labs, and research and development labs. A schematic of the HVTN Laboratory Program is shown in Figure 4.

Dr. Julie McElrath will serve as the Principal Investigator and the overall Director of the HVTN Laboratory Program. Dr. McElrath, who is Professor of Medicine at the University of Washington and Member at the FHCRC, has been associated with the AVEG/HVTN as a site PI since 1992; she has directed the research program of the HVTN Laboratory Program since 2000 and has been head of the Laboratory Program since 2003. The scientific program of the HVTN Laboratory Network consists of a series of integrated laboratories that specialize in the wide scope of laboratory assays required for the evaluation of HIV vaccines.

1. Immune Monitoring Laboratories

The HVTN's approach to evaluation of vaccine immunogenicity has evolved over the past years from a mixed centralized/decentralized system involving several academic labs linked with domestic clinical vaccine units to a cen-

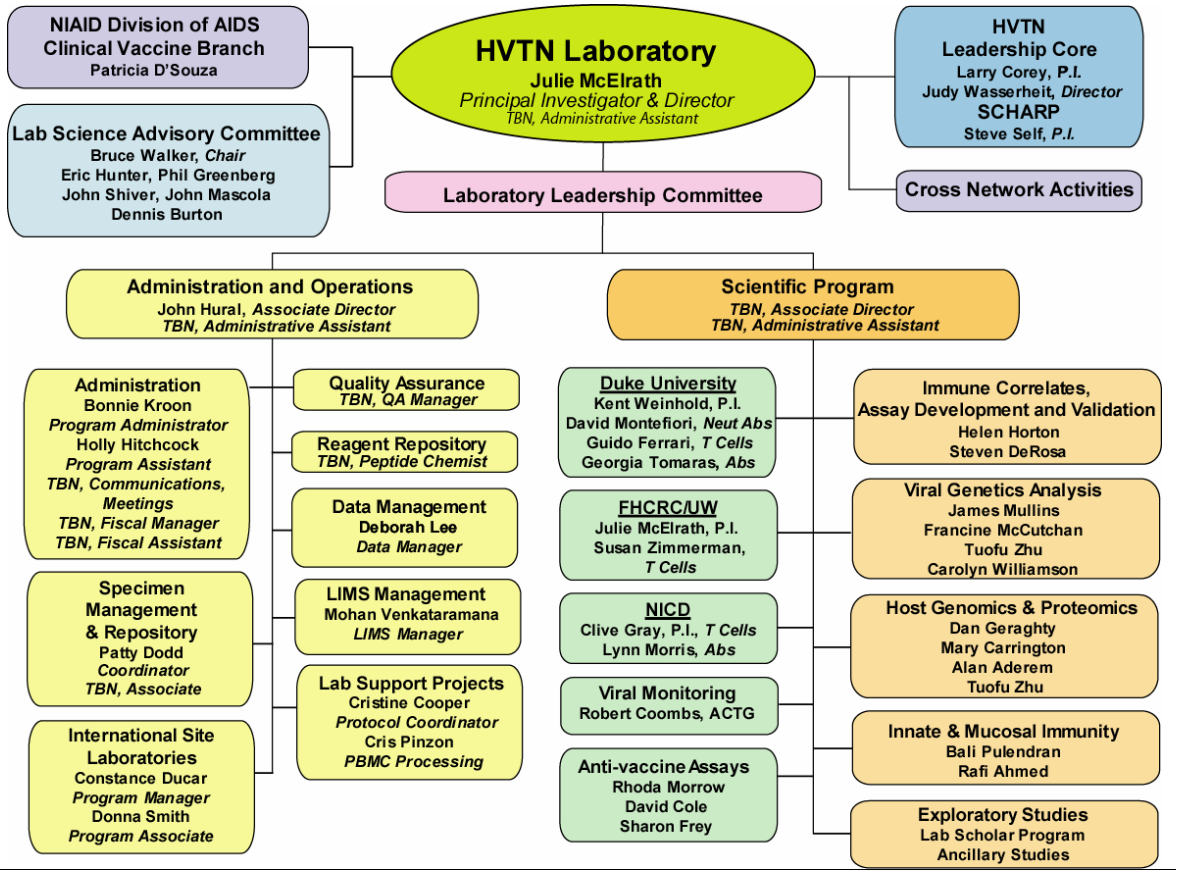
tralized monitoring system in a small number (1-3) of GLP laboratories. This centralization arose from a mandate from DAIDS to ensure that HVTN data met FDA requirements for candidate vaccines in critical pathways for efficacy evaluation. The current model is strongly aligned with laboratory practices of pharmaceuticals and vaccine sponsors, and was successfully implemented through the activities of a strong QA program led by John Hural PhD, Associate Director of the Laboratory Operations and Administration Division, in and collaboration with Dr. Patricia D'Souza at DAIDS. All the Network Laboratories chosen have documented that they can perform a broad range of assays at the highest quality and efficiency, and have the capacity to expand efforts when necessary to meet the demands and pace of the HVTN.

The HVTN will establish 3 immune monitoring laboratories (Figure 4) to apply sensitive, validated assays to characterize HIV vaccine-induced memory T cell and antibody responses. The laboratories at Duke University (Kent Weinhold, PI) include T cell analyses by IFN-γ ELISpot (Guido Ferrari), HIV binding Abs (Georgia Tomaras) and HIV neutralizing Abs (David Montefiori). The T cell laboratory based at FHCRC (Julie McElrath, PI) performs both IFN-γ ELISpot and intracellular cytokine staining. Our international laboratory in Johannesburg, NICD (Clive Gray, PI) performs IFN-γ ELISpot (Clive Gray) and binding and neutralizing Ab assays (Lynn Morris).

a. Duke University Laboratory

The Duke Laboratory is structured around 5 investigators and their research staff, all of whom have extensive experience with their particular assay technologies. The Laboratory Director, Dr. Kent J. Weinhold, is responsible for the overall laboratory administration, immunologic testing, and data reporting. Dr. Georgia Tomaras directs the performance of all protocol-mandated binding antibody studies, including the measurement of serologic responses against vaccine immunogens, and mucosal responses, as well as the induction of antibody responses against specific vaccine vectors (eg, adenovirus). Dr. David Montefiori directs the laboratory assessment of HIV-specific neutralizing antibodies elicited in response to vaccine immunogens. His laboratory has served as a reference for standardized neutralizing Ab responses in immunopathogenesis studies worldwide. Cellular studies of vaccine immunogenicity, presently focused on the IFN-γ ELISpot technology, are conducted under the supervision of Dr. Guido Ferrari. Lastly, the Duke Endpoints Laboratory also houses a dedicated Quality Assurance/Quality Control Unit directed by Dr. Marcella Sarzotti-Kelsoe. This unit is responsible for approval and document control of all training, building, and assay SOPs as well as strict assurance of all levels of GLP compliance within the testing laboratories. The Duke Endpoints Laboratory is housed in the Surgical Oncology Research Facility (SORF), containing approximately 16,000 ft^2 of laboratory space, one-half of which is maintained as

Figure 4. Organization of the HVTN Laboratory Program.



BSL-3 containment laboratories.

b. Fred Hutchinson Cancer Research Center Laboratory

The FHCRC Laboratory focuses on assessment of vaccine-induced T cell responses under the direction of Dr. Julie McElrath. Dr. Susan Zimmerman, trained in basic immunology and with previous industry experience in vaccine development and evaluation, leads the immune monitoring laboratory and oversees the performance of IFN-γ ELISpot and ICS by 4- and 6-color flow cytometry. This laboratory is adjacent to the R&D laboratory, which allows efficient transfer of new assays for immune monitoring, such as multiparameter flow cytometry (MFC) led by Steven DeRosa and functional profiling led by Dr. Helen Horton. The laboratory will relocate in early Fall 2005 to a new facility containing 6000 ft^2 of BSL2 and BSL3 space dedicated for GLP studies and R&D. The FHCRC Shared Resource Facility will be housed on the same floor for additional collaborative studies in genomics and imaging. This laboratory (2nd floor) is in the same building as the HVTN LOAD (5th floor), Core Leadership (5th floor) and SCHARP (4th floor).

c. National Institute of Infectious Diseases Laboratory (NICD)

The NICD Laboratory conducts cellular and humoral immune monitoring assays for most specimens obtained in southern Africa. HVTN-related activities at the NICD take place in the laboratories of Drs. Clive Gray and Lynn Morris. Dr. Gray is responsible for all aspects of the overall laboratory administration, immunologic testing, and data reporting. Evaluation of cellular responses to the vaccine products, presently focused on the IFN-γ ELISpot technology, are conducted under his supervision. His laboratory has been audited by the HVTN Laboratory Operations Division and the DAIDS/PPD and has successfully participated in the HVTN ELISpot proficiency panel comparison study. Dr. Gray's laboratory also conducts some of the specimen processing tasks for southern Africa. His lab has acquired SANAS (national) accreditation for the ELISpot assay and specimen processing. Dr. Lynn Morris directs the performance of most protocol-mandated HIV-binding antibody studies and assessment of HIV-specific neutralizing antibodies elicited in response to vaccine immunogens for specimens from this region. Dr. Morris collaborates extensively with Drs. Montefiori and Tomaras at the Duke University laboratory to ensure that all processes surrounding evaluation of humoral responses are sufficiently standardized. The NICD also houses an onsite quality assurance department that controls all SOPs, conducts regular quality audits of the laboratories and will internally accredit any in-house process that satisfies the necessary quality control requirements.

d. HIV Serology and Viral Monitoring

Volunteers are screened for HIV-1 infection by licensed HIV-1 EIA prior to study enrollment at CLIA/CAP certified laboratories associated with the clinical vaccine units. During the trial and in long-term follow-up, volunteers undergo HIV-1 testing through a centralized laboratory. This maintains blinding at the site and with the study participant, since HIV-1 Abs may emerge during the trial as a result of vaccination. In the past grant period these assays were performed at the California State Laboratory in Richmond, CA. In this grant period we will centralize this testing with the ACTG network laboratory directed by Robert Coombs MD PhD, Professor of Laboratory Medicine at the University of Washington. Dr. Coombs is head of the Laboratory Program of the Adult ACTG, and directs a CAP-certified laboratory that performs HIV-1 testing and monitoring. His laboratory will also perform viral load testing on breakthrough infections and will prepare titered viral stocks from primary transmitted isolates. In addition, through the ACTG-associated laboratories, we will have the ability to assess antiretroviral resistance genotypes and phenotypes.

e. Antivector Immunogenicity

As several HVTN studies stratify enrollees by their antivector immune status, access to such testing is needed for the conduct and analysis of HVTN studies. The adenovirus antibody assay will be performed in Dr. Rhoda Morrow's laboratory at the University of Washington Department of Laboratory Medicine. Dr. Morrow heads the virology diagnostic laboratory at Seattle Children's Hospital and has many years of experience performing FDA-approved and CAP-certified Ab studies for the NIAID-supported HSV vaccine trials in a GLP setting. Drs. Robert Belshe and Sharon Frey at St. Louis University will perform anti-vaccinia neutralizing Ab assays when such studies are needed for trials involving recombinant poxvirus immunogens.

f. HLA Typing Laboratory

Molecular class I and II HLA typing for HVTN study participants will be performed in Dr. Dan Geraghty's laboratory at FHCRC. The FHCRC houses the worlds largest bone marrow transplant program and innovative molecular typing assays have been established at the Center.

2. Research and Development Laboratories

a. Host Genomics and Proteomics

One of the stipulated scientific areas in the RFA for the HVTN is to evaluate the influence of host genetics on vaccine responses. The HVTN has established collaborations with 3 major centers of investigation in host genetic responses to infectious diseases: the laboratories of Drs. Mary Carrington at the National Cancer Institute, Dan Geraghty at FHCRC, and Alan Aderem at the Institute for Systems Biology. These laboratories will participate in selected studies to evaluate host responses to vaccines and, in particular, to evaluate host responses as a correlate of protection in HVTN vaccine efficacy trials. Drs. Carrington and Geraghty's laboratories will explore KIR and various HLA markers while Dr. Aderem will evaluate TLR and SNP analysis.

b. Innate and Mucosal Immunity Laboratories

As discussed extensively in the CORE Research Plan, there is a critical need to develop innovative assays to measure innate and mucosal immune responses after vaccination. We have enlisted the collaboration of Drs. Rafi Ahmed and Bali Pulendran of Emory University to develop assays of innate immune responses after vaccination. They will also focus on alterations of the phenotypic and functional properties of innate immune effector cells (eg, DC, NK cells) as a result of stimulation with various candidate adjuvants, and determine the impact of these responses on adaptive T and Ab responses. Once assays are developed that are reproducible, we will deploy them into the HVTN protocol laboratory studies. They will also work in close collaboration with Dr. McElrath's FHCRC lab to develop and optimize methods to measure mucosal T cell immune responses either by direct sampling or through investigation of mucosal homing markers on PBMC. Simultaneously, Dr. Georgia Tomaras will develop improved, validated assays for measurement of mucosal Ab.

c. Viral Sequencing and Genetic Analyses

Our viral sequencing and genetic analyses team will assess strain diversity of breakthrough infections and viral sequence evolution post-infection as a result of vaccination. These studies will also assess the impact of the immune responses generated by vaccination on the transmitting strains. Whole genomic sequences will be performed in the laboratory of Dr. Francine McCutchan at the USMHRP; the laboratories of Dr. James Mullins at the University of Washington and Dr. Carolyn Williamson at the University of Cape Town will conduct the studies evaluating the influence of vaccination on viral evolution among breakthrough infections. Dr. Tuofu Zhu's laboratory at the University of Washington will evaluate whether vaccination influences reservoirs of HIV in PBMC and purified populations of CD4+ T cells and monocytes.

3. Committees

a. Laboratory Sciences Advisory Committee (External)

The Laboratory Sciences Advisory Committee (LSAC) is an external body of experts charged with critically evaluating the Laboratory Program. The members of the LSAC (Figure 4) bring comprehensive expertise in HIV vaccine research, development and clinical trials. The LSAC reviews the field relevant to vaccine studies, assesses the progress of the Immune Monitoring and Research and Development Laboratories, and formulates recommendations for the scientific direction and future activities of the Laboratory Program. The LSAC meets twice yearly and attendees include NIH/DAIDS representation, the PI of the Network Laboratory Program, and the Associate Director of Laboratory Operations. The meetings are also attended by Drs. Corey, Self and Wasserheit to ensure that the recommendations of this advisory committee are communicated directly to the HVTN SSC. This advisory committee has increased the scientific standards of the HVTN laboratories to very high levels and its frequent meetings and intensive agenda and review will be continued.

b. Laboratory Leadership Committee

During this grant period, the Laboratory Program will initiate a Laboratory Leadership Committee. This committee will consist of the PI and Associate Directors of the Laboratory Program and the scientific leaders of each of the laboratories described above. The DAIDS project officer to the Laboratory Program will serve as an *ex officio* member of this committee. This committee will meet monthly by conference call to provide scientific direction to the HVTN laboratory program and set the milestones and timelines for each component of the Laboratory Program. The HVTN Laboratory will harmonize efforts with the HVTN Leadership CORE and SCHARP to provide seamless coordination of the HVTN's laboratory activities with other Network activities.

4. HVTN LABORATORY OPERATIONS AND ADMINISTRATION DIVISION (LOAD)

The Laboratory Operations and Administration Division (LOAD), headed by Dr. Hural, will function as the central management and communications hub within the Laboratory Program, throughout the HVTN and across other networks. The LOAD will be responsible for overall coordination of the Laboratory Program activities, including communications, recruitment and hiring of scientific and operations personnel, meeting planning, progress reports and interactions within the HVTN and DAIDS. A Laboratory Protocol Coordinator will work with the HVTN protocol teams and vaccine sponsors from the initiation of concept sheets to full protocol development and implementation. This will ensure that the protocol language and appendices correctly describe the immunologic, virologic and safety endpoint assays as well as the timepoints and blood draws for these assays. All laboratory studies performed in support of HVTN protocols, unless designated exploratory or ancillary, are performed in laboratories that are functioning under GLP or CLIA guidelines. The Quality Assurance Program in LOAD will be responsible for monitoring the laboratory performance sites, including assay validation, proficiency studies and overall QA.

Conducting clinical trials in the international setting provides unique challenges for the HVTN. For this reason we have implemented 2 positions, the International Laboratory Program Manager and the International Laboratory Program Associate, who will monitor and address all aspects of quality and training for non-US laboratories.

An extensive series of experiments have shown that accurate assessment of T cell immunogenicity requires quality controlled PBMC processing done at the trial site. As such, the HVTN has in the last year established site-affiliated laboratories to process volunteer specimens within 6 hours of acquisition. After processing and freezing, the specimens are shipped to a redistribution repository. All HVTN sites have in the last 8 months initiated such a program; the HVTN Lab Program has established SOPs and trained site personnel on these procedures and installed a specimen tracking system that provides the logistical support to accomplish this task. The Laboratory Program will continue to oversee the training and monitor the performance of site lab personnel through proficiency testing. They will also take responsibility for overseeing all aspects of specimen requests, transport, and location. The Specimen Management Coordinator will have access to the necessary database information to allow tracking of specimens and chain of custody between the sites, repository and laboratories. The HVTN has established a LabWare laboratory information management system (LIMS) for specimen monitoring and analytical data storage.

E. HVTN Scientific Committees, Working Groups And Advisory Committees

The functions of the HVTN scientific committees, working groups, and advisory committees are integral to the scientific agenda of the organization (Figure 1) and are where the members of the Leadership, Statistical, and Laboratory Programs interact to develop and formalize the HVTN's scientific efforts and processes. The function of these committees is detailed in the CORE Research Plan. This section provides a brief description of each committees' composition and a basic description of its role in the HVTN.

1. PHASE I/II TRIALS COMMITTEE

The Phase I/II Committee is responsible for the scientific and operational oversight of the HVTN's Phase I/IIA trials program. It prepares and regularly updates a Phase I/II scientific agenda and submits the scientific agenda to the SSC for review. The Committee sets criteria for developers for entering the HVTN system, reviews proposals from prospective development partners and advises the HVTN PI and Director, and the Scientific Administration Group (SAG) on promising candidates. The HVTN Phase I/II Committee is chaired by Dr. Scott Hammer, Chief, Division of Infectious Diseases, and Harold C. Neu Professor of Medicine, Columbia University, College of Physicians & Surgeons. It is co-chaired by 3 investigators with extensive, complementary expertise in early phase HIV vaccine trials. Dr. Glenda Gray, Founder and Co-Director of the Perinatal HIV Research Unit at Chris Hani Baragwanath

Hospital, University of the Witwatersrand, Johannesburg, South Africa; Dr. Michael Keefer, Associate Professor of Medicine, University of Rochester, School of Medicine & Dentistry, and Dr. Kent Weinhold, Professor of Immunology and Surgery, Duke University. Additional Phase I/II Committee members include 5 international and 5 US PIs elected by the HVTN investigators; 1 community representative who is elected by the Global CAB, and representatives of each of the HVTN Leadership Group components, and of DAIDS. The inclusion of liaison members on the Phase I/II Committee ensures close, functional linkages with relevant committees and working groups, including the Pharmacy Committee, the Site Development, Management and Clinical Care Committee, the Clinic Coordinators Working Group, and the working groups involved in the development of efficacy trials.

2. HVTN WORKING GROUPS

During the initial funding period the HVTN had a Phase III committee as its other major scientific committee. To more effectively address the complexity of Phase III trials, this committee have been reorganized into working groups; each working group focuses on specific scientific issues and report directly to the SSC. This allows more direct communication between each scientific team and the HVTN's decision-making body.

Each working group is charged with developing a strategic plan for its area of scientific expertise. All working groups are encouraged to draw on expertise outside the HVTN and develop partnerships with other organizations involved in their area of interest. HVTN working groups meet in person at least twice yearly and by conference call as needed. Their progress and agendas are monitored at HVTN Management Team meetings and through reports made periodically to the SSC.

a. Adolescent Trials Working Group (ATWG): The HVTN established an Adolescent Working Group in 2003 to initiate discussions on the complex and often sensitive ethical, regulatory, operational and community issues involved in enrolling minors in HIV vaccine trials.

b. IDU Trials Working Group (ITWG): The IDU Trials Working Group is mandated with developing the strategic plan for conduct of efficacy trials in IDU populations worldwide and will provide essential input on trial design and site selection.

c. Efficacy Trials Design Working Group (ETDWG): The Efficacy Trials Design Working Group is mandated with developing a strategic plan for the design and analysis of all efficacy trials conducted by the HVTN, including the following issues: trial design; criteria for advancement to proof-of-concept or Phase III trials, analyses of correlates of protection, how to deal with the effects of concurrent prevention interventions (eg, PrEP), strategies to predict seroincidence, and detection of transient HIV infection or vaccine-induced seropositivity.

d. Risk Assessment Working Group (RAWG): The Risk Assessment Working Group is charged with proposing standardized approaches to risk reduction counseling and assessment of participant risk behaviors during trials. It will facilitate the adaptation of counseling and assessment tools to the diverse socio-cultural settings across HVTUs to minimize the impact of site-specific effects on analysis and interpretability of efficacy trial data.

e. Clinic Coordinators Working Group (CCWG): The HVTN has an active Clinic Coordinators Working Group, which involves clinic coordinators from all sites and serves as a forum for trouble-shooting the logistics of protocol operations. It is convened monthly by conference call.

f. Community Education and Recruitment Working Group (CERWG): The Community Education and Recruitment Working Group, which includes all HVTN Community Educators and Recruiters, is convened monthly by conference call to address a range of operational needs related to preparing communities for HIV vaccine trials and optimizing recruitment of volunteers.

3. RESOURCE COMMITTEES

Resource committees are standing structures devoted to improving the operational aspects of the HVTN. They are staffed by full-time members in the HVTN Seattle offices but chaired by site PIs and investigators. As the functions of the resource committees are detailed in the CORE Research Plan, this narrative is only a brief description of the committees' function.

a. Performance Evaluation Committee (PEC): The PEC is responsible for evaluating all aspects of the Network: the clinical research sites, the Leadership CORE, the SDMC, and the Laboratory Program.

b. Site Development, Management and Clinical Care Committee (SDMCC): The Site Development, Management and Clinical Care Committee (SDMCC) will coordinate the identification, development and management of HVTN sites, and resolution of any operational or clinical issues arising at HVTUs. This committee will be convened monthly by conference call and includes representation from DAIDS and from HVTUs in the Caribbean, Latin America, Africa and Asia, as well as staff from CORE and the SDMC.

c. Pharmacy Committee: The HVTN will establish a Pharmacy Committee, co-chaired by the HVTN Vaccine Trial Pharmacist and a representative of DAIDS Pharmaceutical Affairs Branch (PAB), that will facilitate communication among HVTN pharmacists about ongoing and upcoming trials, address important pharmacy-related issues that cross-cut specific studies, and identify relevant training needs.

d. Quality Assurance & Data Management Committee (QA/DMC): To increase the Network's capacity to monitor regulatory and protocol compliance and data quality, the HVTN will establish a joint Quality Assurance and Data Management Committee (QA/DMC) to oversee all aspects of quality assurance, including those relevant to data management. The membership, which includes quality assurance and data management personnel at three sites and in each of the components of the HVTN's Leadership Group and a DAIDS representative, will convene quarterly.

e. Training and Education Committee (TEC): The HVTN has, of necessity, established a vaccine trials-specific training program focused on standards for scientifically rigorous, ethically sound research, and regulatory requirements. The Training and Education Committee (TEC) plays a central role in identifying training needs and coordinating the development of training materials, curricula, courses and mentoring relationships. Its members, including site and CORE staff, and representatives from DAIDS and the Fogarty International Center, meet monthly by conference call and semi-annually in person.

f. Conflict of Interest Subcommittee: The Conflict of Interest Subcommittee oversees the implementation of the HVTN Financial Disclosure and Conflict of Interest Guidelines. Specifically, this subcommittee is responsible for reviewing significant interests disclosed by Network members, determining whether a potential conflict of interest exists, and approving proposed plans to mitigate such interests. The subcommittee is composed of the 2 elected at-large investigator members of the SSC.

g. Publications Committee: The Publications Committee convenes as needed by conference call to coordinate internal review of publications involving data from HVTN trials. The co-chairs review all manuscripts and abstracts, and solicit external reviews by Network investigators.

4. ADVISORY COMMITTEES

The HVTN has 4 standing advisory committees of luminary investigators both within and outside the US who review the HVTN overall scientific agenda and course and a study safety monitoring board.

a. The External Advisory Committee (EAC) is composed of a group of eminent, senior scientists with a broad spectrum of scientific and operational expertise related to HIV vaccine development and clinical trials. The EAC members, who are not affiliated with the HVTN, meet annually and at ad hoc sessions, to review the Network's direction and progress. The EAC advises the SSC and serves as an outside reviewer for the use of discretionary funds in general, and specifically for discretionary fund applications over $250,000. These reviews are performed by teleconference.

b. Global Community Advisory Board (GCAB): The Global Community Advisory Board (GCAB) fosters community involvement, provides the SSC with information on community issues, advises on trial design in relation to participant concerns, keeps local CABs apprised of HVTN activities, assists in the development of educational programs and builds collaboration with other prevention efforts and educational campaigns. The GCAB, composed of representatives from each local HVTU CAB and 2 at-large representatives, meets monthly by conference call.

c. Laboratory Sciences Advisory Committee (LSAC): Described above.

d. Safety Monitoring Board: An independent group of clinicians and scientists with expertise in clinical trials that reviews unblinded safety data from HVTN trials. It is chaired by Walter Dowdle PhD.

III. SUMMARY

The HVTN is an international scientific organization focused on the development of a safe, effective vaccine for the prevention of HIV infection on a global scale. In support of this goal, the HVTN has developed an administrative organization and committee structure to ensure efficient progress while fostering the creativity of its scientific contributors. This framework also includes an effective integration of the clinical trials, statistical, and laboratory programs, and has been made a model for clinical trials organizations participating in the Global Vaccine Enterprise. This application builds on the successes of the HVTN and proposes improvements in structure to accommodate the expanding pipeline of HIV vaccine candidates being tested in our partnership with NIAID.